INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61L 33/00

A1

(11) International Publication Number: WO 93/05825

(43) International Publication Date: 1 April 1993 (01.04.93)

(21) International Application Number: PCT/US92/07661

(22) International Filing Date: 10 September 1992 (10.09.92)

(30) Priority data:
07/764,554 20 September 1991 (20.09.91) US

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(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PROCESSES FOR REDUCING THE THROMBOGENICITY OF BIOMATERIALS

(57) Abstract

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International Bureau

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PROCESSES FOR REDUCING THE THROMBOGENICITY OF BIOMATERIALS

Field of the Invention

The present invention relates generally to processes for improving the biocompatibility of polymeric materials. More particularly, the present invention provides processes for reducing the thrombogenicity of biomaterials by directly bonding heparin to blood contacting surfaces of biomedical devices. Advantageously, the processes of the present invention utilize ionizing radiation to sterilize biomedical devices and bind heparin to their blood contacting surfaces.

Description of Related Art

During the past several decades, synthetic polymers have found increased utility as the primary material in the fabrication of medical devices. In conjunction with this increased utility, significant advances in therapeutic and diagnostic procedures utilizing medical devices have provided the catalyst for an emerging biomaterials technology. A major effort in this field of biomaterials technology has been directed toward developing biomaterials having improved blood compatibility.

Synthetic materials such as relatively high molecular weight polymeric materials are foreign to living organisms and when used in direct contact with blood, these material induce blood coagulation and cause thrombus or clot formation. Certain types of materials have a greater tendency to form thrombi and are less biocompatible than other materials. Nevertheless, all foreign materials will induce clot formation to some extent. Thus, medical devices such as synthetic vascular grafts, cannulas, blood indwelling monitoring devices, artificial kidneys, artificial heart-lungs, extracorporeal circuits for auxiliary circulating devices, A-V shunts, vascular

prostheses, artificial heart valves, temporary blood by-pass tubes, and dialysis membranes are inherently thrombogenic. Any thrombi which form on the surface of these devices can stop blood flow or break away and move with the blood current. In vivo applications, the thrombi can cause complications such as pulmonary thrombosis, cerebral thrombosis or myocardial infarction.

One approach to reducing the incidence of thrombus formation on the surface of medical devices is to systemically administer an anticoagulant such as heparin, coumarin or sodium citrate to the patient prior to implanting a medical device or bringing the patient's blood into contact with a device. A major disadvantage associated with this approach is that it significantly prolongs the patient's blood clotting time. Should the patient be injured with either external or internal bleeding, the consequences of a prolonged clotting time can be a serious excessive loss of blood before sufficient clotting takes place to stop the bleeding.

Another approach to solving the problem associated with the thrombogenicity of medical devices is to alter the surface of the blood contacting surfaces to reduce thrombogenic activity. In particular, a number of researches have attempted to physically or chemically bind heparin to the surface of biomaterials in order to reduce thrombogenicity. Since heparin is a highly hydrophilic mucopolysaccharide and insoluble in organic solvents, in order to coat a solid surface with heparin it must be applied from an aqueous solution. Polymeric materials, on the other hand are largely hydrophobic and aqueous solutions applied to these surfaces bead-up and fail to form even, continuous films. Thus, attempts to physically bind heparin to these hydrophobic surfaces result in uneven and ineffective applications. Moreover, for the same reason, attempts to chemically bind heparin to polymeric

surfaces result in the same uneven and nonuniform heparin deposits.

Other attempts to bind heparin to hydrophobic polymeric surfaces include first coating the biomaterial surface with a hydrophilic material which is soluble in organic solvents. Then, an even heparin coating can be applied directly to the hydrophilic surface. Additionally, some researchers have covalently bonded heparin to the hydrophilic coating by selecting a hydrophilic coating having functionalities which are reactive to heparin. This approach to improving the blood compatibility of biomaterials has generally not met with success. The hydrophilic pre-coating is not covalently bonded to the surface of the biomaterial. Thus, regardless of whether or not the heparin is covalently bound to the pre-coating, the physical link between the pre-coating and the surface of the biomaterial weakens and the heparin escapes from the surface. Moreover, reacting the mucopolysaccharide moiety with the hydrophilic coating alters the mucopolysaccharide, resulting in a reduced activity.

Additional attempts to bind heparin to biomaterial surfaces have focused on providing an association of a hydrocarbon and heparin in order to enhance its ability to physically coat polymeric surfaces. In one of these associations the heparin anion is complexed with an organic cation. This is possible because heparin's mucopolysaccharide structure is anionic with both sulfonic acid and carboxylic acid functionalities. In its sodium salt form, heparin anion can associate with other cations, such as quaternary ammonium cations, capable of exchanging with sodium. Many of these cations have significant hydrophobic features and when associated with the heparin anion will readily dissolve in organic solvents such as alcohols. Films of these heparin associations can be uniformally applied to the surfaces of many polymers used

in medical devices. The integrity and stability of these films however are dependent upon the strength of the association between heparin and the cation. The ionic association of the cation and heparin anion must be sufficiently high to preclude blood from exchanging with the cation-heparin association and removing heparin from the surface of the polymer. The most significant advantage of these heparin associations are that the heparin mucopolysaccharide is not altered in any way and the heparin retains its anticoagulant activity.

Some quaternary ammonium heparin associations have met with approval in the medical community. Notably benzalkonium heparin, stearylkonium heparin and tridodecylmethylammonium heparin associations have relatively high ionic strengths and a significant amount of the associations remain intact in the presence of blood. Additionally, films of these quaternary ammonium salt heparin associations physically adhere to many biomaterials and retain much of their anticoagulant activity. These films can however be removed using mechanical forces and excess handling will cause a significant loss of surface anticoagulant activity.

Another association of a hydrocarbon and heparin is an acid-base complex of the heparin acid functionalities and an organic base. These acid-base complexes have the same advantageous film-forming properties and dissolution properties. Particularly well-known acid-base complexes are dimethylstearylamine heparin and polyethyleneimine heparin complexes.

Many researchers and practitioners within the medical device industry have generally recognized that covalently bonding heparin to the surface of biomaterials is a superior approach to producing antithrombogenic medical devices. A number of techniques have been utilized to covalently link heparin to polymers. One of these involved

milling heparin powder in silicone or applying aqueous solutions of heparin to the surface of silicone devices and then irradiating the device with ionizing radiation. As mentioned above, however, aqueous solutions of heparin do not wet the hydrophobic silicone surfaces. Thus, this method does not provide uniform continuous coatings of heparin and any heparin which may deposit on the surface appears in isolated deposits.

Another covalent bonding technique utilizes polymeric surface grafting processes to provide active chemical functionalities on the polymeric surface which will react with heparin. Then exposing heparin solutions to these functionalities causes heparin to bind to the active functionalities. These techniques, however, result in insufficient surface anticoagulation activity which is attributed to both small amounts of heparin bonded to the surface and heparin modification. The heparin modification occurs because polysaccharide functionalities which contribute to the anticoagulation properties of the heparin are modified when they react with functionalities on the polymeric surface.

Other similar approaches include derivatizing the heparin molecule itself to provide specific reactive functionalities for covalently bonding to the surface of a medical device. For the same reasons described above, this approach also suffers from insufficient anticoagulant activity on the polymeric surface. Believing that part of the reduction in activity may be caused by conformational restraints on the immobilized heparin molecule, some researches have modified heparin to include large spacer molecules or leashes which can be attached to polymer surfaces. This approach also results in a chemically modified heparin polysaccharide having reduced anticoagulant activity.

A common problem associated with all of these attempts

to provide antithrombogenic surfaces for medical devices stems from the fact that any one device is rarely made from a single type of polymer. Thus, effectively developing and manufacturing heparin treated surfaces for all of the polymers utilized in a single device is very costly. Additionally, since all medical devices must be sterilized, antithrombogenic surfaces on polymers must retain sufficient amounts of activity subsequent to sterilization. Most medical devices are sterilized using a gas such as ethylene oxide or ionizing radiation. Thus, the form in which the anticoagulant agent is retained on the surface of the polymer must be sufficiently stable to remain active subsequent to sterilizing and for a reasonable shelf life.

Accordingly, it is the object of the present invention to provide processes for enhancing the antithrombogenic activity of biomaterials and medical devices.

It is also the object of the present invention to provide processes for covalently bonding anticoagulants uniformally to the surface of biomaterials and medical devices.

It is additionally the object of the present invention to provide processes for simultaneously sterilizing and enhancing the antithrombogenic activity of medical devices.

It is further the object of the present invention to provide anticoagulant bonding processes which do not cause significant loss in anticoagulant activity.

It is also the object of the present invention to provide biomaterials having sustained antithrombogenic activity in the presence of blood and other high ionic strength fluids.

SUMMARY OF THE INVENTION

In its broadest aspect, the present invention accomplishes the above objectives by providing processes for chemically binding anticoagulants to biomaterials. The

processes of the present invention are directed toward chemically binding heparin to surfaces of biomaterials in order to provide medical devices which can be used in direct contact with blood without causing platelet aggregation and the formation of thrombi. Moreover, heparin which is bonded to medical devices in accordance with the present invention retains significant anticoagulant activity and does not leach, hydrolyze or otherwise dissociate from the surface of medical devices.

More particularly, the present invention provides methods for reducing the thrombogenicity of biomaterials by providing biomaterials having a surface coating of anticoagulant and exposing the coated biomaterials to sufficient ionizing radiation to chemically bind the anticoagulant to the biomaterial. Preferably, the anticoagulant coating is a uniform continuous film of heparin. Additionally, the heparin is preferably an association of the heparin anion and an organic compound. Suitable organic compounds are organic cations such as quaternary ammonium sales and organic bases such as amines. Many ionic complexes of heparin and quaternary ammonium cations are commercially available from a number of sources. Others can be prepared by combining sodium heparin and the selected quaternary ammonium salt in appropriate solvent and collecting the precipitated ionic complex. Similarly, organic amines readily form an acid-base complex with heparin by combining a solution of heparin with a solution of the appropriate amine.

Further, in accordance with the present invention, providing biomaterial having an anticoagulant coating can be accomplished by allowing the biomaterial to contact organic solvent solutions of the ionic complex in order to deposit a film of the solution on the surface of the biomaterial. Typically, the liquid solutions include the ionic complex in a volatile organic solvent which readily

vaporizes at ambient temperatures and pressures leaving a coating of the ionic complex on the surface of the biomaterial.

After allowing the solvent to vaporize, exposing the coated biomaterial to ionizing radiation can be accomplished using any ionizing radiation source including gamma radiation sources, electron beam sources, and x-ray sources. Although, radiation doses of as low as 0.1 megarads are sufficient to chemically bond heparin to polymeric biomaterials, it is common to use higher sterilizing doses of radiation. This advantageously provides a sterile biomaterial and the anticoagulant activity of the bonded heparin remains sufficiently high even after exposure to the higher radiation doses.

As a feature of the present invention, following exposing the coated biomaterials to ionizing radiation, the processes of the present invention can further include contacting the coated biomaterial with a high ionic strength salt solution. As described in more detail below, this step results in the exchange of the cation of the ionic complex with a much less toxic cation of the salt solution. Moreover, the process can further include exposing the coated and exchanged biomaterial to sterilizing doses of ionizing radiation without significantly reducing the anticoagulating activity of the surface of the biomaterial.

Advantageously, the thrombogenicity of medical devices fabricated from a variety of biomaterials can be reduced in accordance with the teachings of the present invention. There is no need to treat each of the biomaterials differently since the teachings of the present invention apply to polymeric biomaterials generally.

Further objects, features and advantages of the processes of the present invention, as well as a better understanding thereof, will be afforded to those skilled in

the art from a consideration of the following detailed explanation of preferred exemplary embodiments thereof.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention provides processes for reducing the thrombogenicity of medical devices by chemically binding anticoagulant to the surfaces of biomaterials utilized in medical devices. The invention disclosed herein is described in terms of chemically binding heparin to the surfaces of polymeric materials having utility as biomaterials in fabricating blood contacting surfaces of medical devices. Those skilled in the art, however, will appreciate that the processes taught herein are applicable to chemically binding polysaccharides, mucopolysaccharides, glycoproteins, and related compounds to polymeric materials in general.

The present invention is based upon the surprising discovery that materials which are first coated with organic solutions of heparin and then exposed to ionizing radiation, retain high antithrombogenic activity even after being subjected to severe techniques for removing the heparin from the surface. In accordance with the present invention, biomaterials can be uniformally and continuously coated with heparin without modifying or derivatizing the mucopolysaccharide moiety. Accordingly, the heparin mucopolysaccharide moiety remains intact and its anticoagulant activity is not compromised.

More specifically, the present invention provides methods for reducing the thrombogenicity of polymeric materials by providing polymeric material having a coating of heparin and exposing the coated polymeric material to sufficient ionizing radiation to chemically bind the heparin to the polymeric material. In accordance with the process of the present invention, providing a coating of heparin is accomplished by contacting the surface of the

polymeric material with an organic solvent solution of heparin for a length of time sufficient to deposit an anticoagulating amount of heparin on the surface of the polymeric material. Subsequent to contacting the surface of the polymeric material with an organic solvent solution, the solvent is allowed to vaporize from the polymeric material. Then exposing the coated polymeric material to ionizing radiation is typically accomplished with standard gamma irradiation sterilizing procedures using cobalt^{60} or cesium^{137} sources. However, other types of ionizing radiation such as electron beam and x-rays are also applicable.

Polymeric materials having utility in the present invention are solid organic polymers in the form of shaped articles, powders, granules, pellets, films, fibers or foams. Preferably, the polymeric materials are biomaterials in the form of medical devices used for in vivo, ex-vivo and in vitro diagnostic and therapeutic procedures. Examples of these include blood contacting medical devices such as synthetic vascular grafts, catheters, cannulas, blood indwelling monitoring devices, artificial kidneys, artificial heart-lungs, extracorporeal circuits for auxiliary circulating devices, A-V shunts, vascular prostheses, artificial heart valves, temporary blood by-pass tubes, and dialysis membranes.

Additionally, polymeric materials having utility in the practice of the present invention retain sufficient physical integrity to perform their intended function following exposure to ionizing radiation in amounts sufficient to chemically bind heparin. As described in more detail below, the amount of ionizing radiation received by the polymeric material can vary, but is typically at least 1 megarad. Suitable polymeric materials include polyvinylchloride, polycarbonate, polypropylene, silicone, polyurethane, polyester, polyethylene,

polysulfone, nylons, cellulose, and acrylate materials. Preferred polymeric materials are polyvinylchloride, silicone, polycarbonate, polyethylene, polypropylene and polyester materials.

In accordance with the present invention, suitable forms of heparin are organic compound-heparin complexes in which the organic compound has sufficient hydrophobic or lipophilic properties to render heparin soluble in organic solvent. One type of organic compound-heparin complex having utility in the present invention is an acid-base complex of organic base-heparin acid in which the acidic moieties of the heparin mucopolysaccharide and a suitable organic base form an acid-base complex. Primary, secondary, or tertiary amines are organic bases known to form acid-base complex with heparin. Particularly suitable organic bases are dimethylstearylamine and polyethyleneimine which form dimethylstearylamine-heparin and polyethyleneimine-heparin, respectively, with heparin.

Other suitable organic compound-heparin complexes having utility in the present invention are ionic complexes of organic cation-heparin anion in which the heparin mucopolysaccharide anion and a suitable organic cation form an ion pair. Particularly suitable organic cations are cations of quaternary ammonium salts including benzalkonium, stearylkonium, and tridodecylmelthylammonium cations. In accordance with the present invention, preferred organic compound-heparin complexes are benzalkonium-heparin, stearylkonium-heparin, and tridodecylmethylammonium-heparin.

Many of the quaternary ammonium-heparin ionic complexes are commercially available. Others can be prepared by combining sodium heparin and the selected quaternary ammonium salt in an appropriate solvent or combination of solvents. The association will typically form quickly and precipitate as an ionic complex of quaternary ammonium-

heparin. For example, benzalkonium-heparin can be prepared by combining aqueous solutions of benzalkonium chloride and sodium heparin. The benzalkonium-heparin ionic complex precipitates cleanly upon formation and the resulting complex dissolves in lower organic alcohols such as isopropylalcohol.

In accordance with the present invention, contacting polymeric material with organic solvent solution of heparin can be accomplished using any of a variety of methods including dipping the polymeric material in the solution, spraying the solution onto the polymeric material, flushing tubing with the solution, dropping solution onto the polymeric material and brushing the solution. Typically the contacting step is carried out for a length of time sufficient to deposit an anticoagulating amount of heparin on the polymeric material. As will be described in more detail below, the amount of heparin deposited on the polymeric material is also dependent upon the concentration of the heparin in the organic solvent solution.

The choice of organic solvent is dependent upon the selected polymeric material and the solubility of the organic compound-heparin complex. Preferably, the organic solvent does not dissolve, or chemically react with the polymeric material. Organic solvents capable of swelling selected polymers are preferred in some applications in which heparin is desirably physically immobilized by swelling the polymer and locking in the heparin. Additionally, the solvent should be nonreactive with the organic compound-heparin complex and preferably has a high vapor pressure for ease in vaporizing the solvent subsequent to dipping, spraying, flushing or brushing. Suitable solvents are lower alkyl alcohols, halohydrocarbons, combinations of halohydrocarbons and alcohols, hydrocarbons, ethers, ketones, dimethylformamide, dimethylsulfoxide, and dimethylacetamide.

Suitable solvents are halocarbons such as 1, 1, 2-trichloro 1, 2, 2, trifluoroethane and combinations of halocarbons and lower alcohols. Particularly suitable solvents are the liquid Freons®, available from DuPont. Of these the preferred solvents are Freon TF® which is 1, 1, 2-trichloro-1, 2, 2, trifluoroethane and Freon TE® which is a combination of ethyl alcohol and 1, 1, 2-trichloro-1, 2, 2, trifluoroethane.

The organic cation-heparin anion complex is typically present in the organic solvent solution at from about 0.01 wt% to about 10 wt%. The preferred concentration depends upon the particular type of polymeric material utilized and the desired amount of heparin coating. The concentration of organic cation-heparin anion complex in the organic solvent solution correlates with the amount of complex which is coated on the polymeric material. Thus, the higher the concentration of the complex, the higher the amount of complex coating. Also, some polymeric materials have surface characteristics which cause higher amounts of complex to coat.

As just mentioned, suitable concentrations of the organic compound-heparin complex can also depend upon the desired amount of organic compound-heparin complex coating on the polymeric material. The preferred amount of coating is an anticoagulating amount and this anticoagulating amount primarily depends upon the specific function of the polymeric material. Polymeric materials utilized as biomaterials in medical devices which function for prolonged periods in contact with blood will preferably have higher amounts of coating. Accordingly, organic solvent solutions utilized to coat these biomaterials will have higher concentrations of complex. Alternatively, to provide more coating, the step of contacting the biomaterials with the organic solvent solution can be carried out a plurality of times. Generally speaking, an

anticoagulating amount of organic cation-heparin anion complex coating on biomaterials is from about 3 micrograms/cM^2 to about 40 micrograms/cM^2. Additionally, for most applications, the preferred concentrations of organic cation-heparin anion complex in organic solvent solution is about 0.5 wt%.

As mentioned above, in accordance with the present invention, the coated polymeric material is exposed to sufficient ionizing radiation to chemically bind heparin to the polymeric material. This amount of radiation can be as low as 0.1 megarads. Moreover, exposing the polymeric material to sterilizing doses of higher than 3 megarads does not significantly reduce the anticoagulant activity of the chemically bonded heparin. Some decrease in heparin activity accompanies exposure to ionization radiation, however, there is no accompanying adverse properties associated with the reduction in activity. Accordingly, as long as the final anticoagulating activity of the polymeric material is sufficiently high for the intended function of the polymeric material and the polymeric material itself is not adversely effected, any dose of ionizing radiation can be used.

Because sterilizing doses of ionizing radiation can be utilized during the exposure step, the present invention also provides processes which simultaneously reduce the thrombogenicity of medical devices and sterilizes the medical devices. Accordingly, forming a coating of an organic solvent and of an organic compound-heparin complex on the medical device, allowing the organic solvent to vaporize, and exposing the coated medical device to ionizing radiation can produce a sterile antithrombogenic medical device with heparin chemically bonded to the surface of the medical device.

As mentioned above, the processes of the present invention are applicable to a variety of polymeric

materials having utility as biomaterials in the fabrication of medical devices. Accordingly, forming a coating of an organic solvent and an organic compound-heparin complex can be accomplished on medical devices which are fabricated from different biomaterials using a single dipping, spraying, flushing or brushing step as previously described. Typically, there is no requirement to treat each type of biomaterial separately. Additionally, although, it is frequently convenient to form the coating of the complex of organic compound and heparin anion in a manner which coats many surfaces of the medical device, the relevant surfaces are the blood contacting surfaces of the medical device. Accordingly, a single extracorporeal circulation device can include a polycarbonate housing and silicone or polyvinylchloride tubing. All of these biomaterials when incorporated in the circulation device have blood contacting surfaces which can be simultaneously coated with heparin by flushing the blood contacting surfaces with a quaternary ammonium cation and heparin anion. A preferred solution is a Freon® solution of about 0.5 wt% stearylkonium heparin.

As mentioned above, organic solvents having utility in the process of the present invention preferably have high vapor pressures. Thus, allowing the organic solvent to vaporize typically occurs very quickly under ambient conditions. However, small amounts of flowing dry nitrogen can hasten the process.

As already mentioned, the preferred organic cation-heparin anion complexes utilized in the practice of the present invention have hydrophobic and lipophilic characteristic which render them soluble in organic solvents. Moreover, the combination of organic solvent and organic cation-heparin anion complex "wets" and coats the polymeric materials and medical devices in a uniform and continuous manner. Thus, subsequent to allowing the

organic solvent to vaporize, an organic cation-heparin anion coating forms which is uniform and continuous. This feature provides medical devices with coated surfaces, and more importantly coated blood contacting surfaces, which are uniformally antithrombogenic. These coatings are unlike prior art "coatings" of nonderivatized heparin which are noncontinuous and nonuniform deposits of heparin.

When it is preferable to simultaneously chemically bind heparin to medical devices and sterilize the medical devices, prior to exposing the medical devices to ionizing radiation, the processes of the present invention further include packaging the medical devices in sterile packaging or packaging suitable for maintaining sterility after a sterilizing procedure. Finally, exposing the medical device to ionizing radiation includes exposing the medical device to sufficient ionizing radiation to sterilize the medical device and chemically bind heparin to the medical device. Typically, total ionizing radiation doses of at least 2.5 megarads are required to meet the standards for sterility. However, doses as low as 1.5 megarads can be used as well.

A particularly advantageous feature of the present invention is based upon the discovery that it is largely the heparin anion which is chemically bonded to polymeric material following the exposure to ionizing radiation. When the heparin complex of the present invention is an organic cation-heparin anion, the organic cation remains ionically associated with the heparin anion and it is not significantly covalently or otherwise directly bonded to the polymer material. Thus, by contacting the coated surfaces of the radiation exposed medical device with liquid solution having an ionic strength sufficiently high to exchange organic cation with a cation in the liquid solution, organic cation can be removed from the medical device without removing heparin anion. This step provides

for exchanging a cation, such as benzalkonium or stearylkonium which has less desirable biocompatible characteristics, for a cation such as sodium having a high degree of biocompatibility.

Thus, an alternative to simultaneously binding heparin to a medical device and sterilizing the medical device is a process which includes forming a coating of an organic cation-heparin anion complex on the medical device and exposing the coated medical device to sufficient ionizing radiation to bind the heparin anion to the medical device. The next steps include exchanging the organic cation with a highly biocompatible cation, packaging the medical device in appropriate packaging for maintaining sterility, and sterilizing the medical device. This sterilizing step is preferably accomplished by exposing the medical device to a total dose of at least 1.5 megarads of ionizing radiation. However, other suitable sterilizing procedures including exposure to sterilizing gases and heat can also be used when applicable.

Liquid solutions having sufficiently high ionic strength include solutions of 20 wt% NaCl and aqueous buffered solutions of surfactants.

In an exemplary embodiment of the present invention, polyvinylchloride tubing can be coated on the interior walls of the tubing by flushing the tubing with a Freon® solution of 0.5 wt% stearylkonium-heparin for 30 seconds and allowing the Freon® to vaporize. Then packaging the tubing in suitable packing and exposing the packaged tubing to from 2.5 megarads to 3.0 megarads of ionizing radiation emitted from a $cobalt^{60}$ source produces sterile polyvinylchloride tubing having nonthrombogenic interior walls.

In another exemplary embodiment of the present invention, silicone tubing can be coated on the interior walls by flushing the tubing with an isopropyl alcohol

solution of about 0.5 wt% benzalkonium-heparin for about 30 seconds. Then exposing the coated tubing to about 1 megarad of gamma irradiation from a cobalt^{60} source produces silicone tubing having chemically bonded benzalkonium-heparin. Then soaking the exposed tubing in an aqueous solution of 20 wt% NaCl exchanges the benzalkonium cation for sodium cation resulting in silicone tubing having chemically bonded sodium heparin.

The mechanism of this binding procedure is not precisely known, however, it is speculated that the radiation causes free radicals to form on both the polymeric material and the heparin. Once formed, if a free radical on the polymeric material is in close enough proximity to a free radical on the heparin, they can combine to form a covalent bond. The required amount of radiation can vary depending upon the type of polymeric material and the amount of heparin coating.

The following non-limiting examples further illustrate methods for preparing the polymeric materials having reduced thrombogenicity as well as present data which substantiates the chemically bonded nature of the heparin.

EXAMPLE 1

Thirty-six polyester blood filter screens were coated with stearylkonium heparin by dripping a controlled amount of a Freon TE® solution of 0.5 wt% stearylkonium heparin onto the filter screens. The amount of solution was controlled so that twelve screens were coated with about 3 micrograms/cM^2, twelve screens were coated with about 10 micrograms/cM^2, and twelve screens were coated with about 32 micrograms/cM^2. Within each group of twelve stearylkonium-heparin coated screens, three of the screens were retained as controls, three were exposed to a total dose of 0.5 Megarads of gamma irradiation, three were exposed to a total dose of 1.0 megarads of gamma irradiation, and three

were exposed to a total dose of 3.0 megarads of gamma irradiation.

Each of the 36 coated polyester blood filter screens was soaked in a saline solution of surfactant for 48 hours to removed all stearylkonium heparin which was not chemically bonded to the polyester. Following this soaking procedure each of the extract solutions was quantitatively analyzed for heparin using an X_a inhibition assay. Using the extract data from the control nonirradiated sample, the amount of heparin bonded to each group of three treated polyester samples was taken as the difference between the heparin found in the control samples and the heparin found in the irradiated sample.

Following the soaking procedure for each sample, the irradiated samples were evaluated for surface immobilized heparin by a thrombin uptake technique. This procedure consisted of exposing the soaked polyester filter screens in a solution of 10 NIH unit/mL thrombin in a saline and surfactant solution for 10.0 minutes. After 10 minutes the thrombin solution was collected and assayed for thrombin. Thrombin uptake is indicative of heparin or anticoagulant activity.

Table I illustrates the results of the X_a inhibition assay for heparin and the thrombin assay. The thrombin assay is expressed as the calculated amount of thrombin uptake in units/cM^2.

TABLE I

SAMPLE	Theoretical amount deposited	Stearylkonium heparin in solution*	% retained on filter	Thrombin uptake
	ug/cm2	ug/cm2 %		U/cm2
	n = 3			n = 3
Control/ no radiation	33.5 ± 0.2	--	0	
0.5 Mrad	3	3.1 ± 0.4	11	0.007
1.0 Mrad	32.2 ± 0.6	37	0.008	
3.0 Mrad	33.2 ± 0.6	9	0.014	
Control/ no radiation	109.2 ± 0.5	--	0	
0.5 Mrad	108.9 ± 0.5	3	0.009	
1.0 Mrad	108.3 ± 0.4	10	0	
3.0 Mrad	108.4 ± 0.1	9	0.027	
Control/ no radiation	3231.8 ± 2.0	--	0	
0.5 Mrad	3227.7 ± 0.6	13	0.007	
1.0 Mrad	3228.8 ± 0.8	9	0	
3.0 Mrad	3224.2 ± 3.3	24	0.027	

* Stearylkonium heparin is expressed in amount in solution based on quantitative heparin assay

The results indicate that active heparin is chemically bonded to the surface of polyester filter screens after exposure to gamma irradiation. The extraction tests show that up to 37% of heparin is not extracted. The thrombin uptake tests indicate that the surface of the polyester retains significant anticoagulating activity after the extraction procedure.

EXAMPLE 2

Twelve pieces of silicone tubing having an O.D. of 1/8" and an I.D. of 1/16" were coated with stearylkonium heparin by flushing and draining the tubing with a Freon TE® solution of 0.5 wt% stearylkonium heparin. Three of the

silicone tubing pieces were used as nonirradiated control samples, three pieces were exposed to a total dose of 0.5 megarads gamma irradiation, three were exposed to 1.0 megarads, and three pieces were exposed to 3.0 megarads. The samples were evaluated by first flushing them with a salt and surfactant extract solution at 100 mL/minute for 2 hours. The salt and surfactant extract solutions were then evaluated for heparin using the X_a inhibition assay. Using the nonirradiated samples as a control, the amount of heparin bonded to each group of three treated polyester samples was taken as the difference between the heparin found in the control samples and the heparin found in the irradiated sample.

The flushed silicone tubing samples were then evaluated for surface immobilized heparin by a thrombin uptake technique. This procedure consisted of pipetting 1.0 mL aliquots of 10 NIH unit/mL thrombin in an albumin-tris saline solution into 56 cM of tubing which was sealed with a sleeve and rotated on a slanted turntable for 10.0 minutes. The thrombin solution was then decanted from the tubing and assayed for thrombin.

Table II illustrates the results of the X_a inhibition assay for heparin and the thrombin assay. The thrombin assay is expressed as the calculated amount of thrombin uptake in units/cM^2.

TABLE II

SAMPLE	Stearylkonium heparin	% retained in tubing extracted	Thrombin uptake
	ug/cm2	%	U/cm2
	n = 3		n = 3
No coating		--	0
Control/ no radiation	25.9 ± 4.9	--	0.007
0.5 Mrad	25.7 ± 4.5	1	0.005
1.0 Mrad	11.3 ± 30.6	56	0.006
3.0 Mrad	0	100	0.018

The results shown in Table II indicate that at 3 megarads substantially all of the heparin is bonded to the silicone. These results are substantiated by the thrombin uptake data.

EXAMPLE 3

Twelve samples each of polyvinylchloride (PVC) tubing having 1/8" O.D. and 1/32" I.D., polypropylene (PP) tubing having 1/8" O.D. and 1/16" I.D., polyethylene (PE) tubing having 2.92 mM I.D. and 3.73 mM O.D., and polyurethane (PU) tubing having 3/16" O.D. and 1/16" I.D. were coated with stearylkonium heparin and evaluated using the same coating and evaluation techniques described for Example 2. Table III illustrates the results of the X_a inhibition assay for heparin and the thrombin assay. The thrombin assay is expressed as the calculated amount of thrombin uptake in units/cM^2.

TABLE III

SAMPLE	Theoretical amount heparin deposited ug/cm2	Stearylkonium heparin extracted	% retained on tubing	Thrombin uptake U/cm2
	n = 3			n = 3
PVC Tubing				
No coating -- Control/		--		0
no radiation 4	2.9	--		0
0.5 Mrad 4	0.8		72	0.005
1.0 Mrad 4	0.6		80	0.012
3.0 Mrad 4	0		100	0.06
PP Tubing				
No coating -- Control/		--		0
no radiation --	17.9 ± 3.0	--		0.007
0.5 Mrad --	16.3 ± 5.4	9		0.006
1.0 Mrad --	16.4 ± 4.6	8		0.008
3.0 Mrad --	16.8 ± 3.5	6		0.009
PE Tubing				
No coating -- Control/		--		0
no radiation --	17.9	--		0.002
3.0 Mrad --	17.5		2	0.003
5.0 Mrad --	15.4	14		0.007
PU Tubing				
No coating -- Control/		--		0.034
no radiation --	17.7	--		0.027
3.0 Mrad --	22.8	-29		0.03
5.0 Mrad --	12.2	31		0.037

The results shown in Table III indicate that heparin binds to polyvinylchloride, polypropylene, polyethylene, and polyurethane tubing after exposure to gamma

irradiation. These results are substantiated by the thrombin uptake data. The thrombin uptake data also show other surface actions from the coating which affect anticoagulating surface activity.

EXAMPLE 4

Twelve polycarbonate connectors were dipped into a Freon TE® solution of 0.5 wt% stearylkonium heparin and dried. Three of the connectors were exposed to a total dose of 0.5 megarads of gamma irradiation, three were exposed to a total dose of 1.0 megarads of gamma irradiation, and three were exposed to a total dose of 3.0 megarads of gamma irradiation. The twelve polycarbonate connectors were then evaluated according to the same procedures described in Example 1. Table IV illustrates the results of the X_a inhibition assay for heparin and the thrombin assay. The thrombin assay is expressed as the calculated amount of thrombin uptake in units/cM^2.

TABLE IV

SAMPLE	Theoretical amount heparin deposited	Stearylkonium heparin extracted	% retained on connector	Thrombin uptake
	ug/cm2	%		U/cm2
n = 3 Polycarbonate Connectors		n = 3		
No coating--		--		0
Control/ no radiation--	0.61 ± 0.10	--		0.021
0.5 Mrad--	0.56 ± 0.10	8		0.019
1.0 Mrad--	0.60 ± 0.14	2		0.018
3.0 Mrad--	0.45 ± 0.04	26		0.014

The results shown in Table IV indicate that polycarbonate will bind heparin after exposure to gamma irradiation. The thrombin uptake data indicate results

similar to that for the polyurethane described above.

EXAMPLE 5

Three pieces of polyvinylchloride tubing having a 1/4" I.D. were flushed and drained with a Freon TE® solution containing 0.5 wt% benzalkonium heparin (BKH). Following coating with benzalkonium heparin, the three tubing pieces were exposed to 3.0 megarads of gamma irradiation. The samples were evaluated using the techniques described in Example 2 above.

Table V illustrates the results for the thrombin assay. The thrombin assay is expressed as the calculated amount of thrombin uptake in units/cM^2.

TABLE V

SAMPLE	Thrombin uptake U/cm^2
PVC Tubing BKH treated	
3.0 Mrad	0.047

The thrombin uptake data results shown in Table V indicate that polyvinylchloride which is coated with benzalkonium heparin, exposed to gamma irradiation and extracted with a high ionic strength solution retains surface anticoagulating activity.

EXAMPLE 6

Ten feet of polyvinylchloride tubing having a 3/8" I.D. was flushed with a Freon TE® solution of 0.5 wt% stearylkonium heparin. The coating step was carried out in such a manner that between 2.4 mg and 3.6 mg of stearylkonium moiety is coating of the PVC tubing. The stearylkonium heparin was labelled on the stearylkonium

moiety with C^{14}. The polyvinylchloride tubing was then soaked in bovine plasma for 24 hours to remove stearylkonium which is not chemically bond. During the 24 hour soak, samples were taken and analyzed for stearylkonium content using a C14 counting method. Two samples were collected at each time interval.

Table VI indicates the results obtained for each sample analyzed for C14 content.

TABLE VI

C-14 SK moiety leaching

Time	SK moiety (mg) leached into bovine plasma	
5 min	1.05, 1.73	
10 min	1.57, 1.47	
20 min		2.57, 2.12
1 hr		2.56, 2.69
2 hr		2.45, 3.08
18 hr		2.71, 4.03
24 hr		2.39, 3.94

The results shown in Table VI illustrate that the stearylkonium moiety is not retained by the surface of the polyvinylchloride by is substantially extracted by the salt solution after 24 hours.

EXAMPLE 7

Thirty strips of diethylhexylphthalate plasticized polyvinylchloride having a surface area of approximately 60 cM^2 were coated with stearylkonium heparin by manually depositing a controlled quantity of a Freon TE® solution of 0.5 wt% stearylkonium heparin on the surface of the strips. Half of these samples were irradiated to a total dose of 3.5 - 4.0 megarads. Table VII details the approximate amount of stearylkonium heparin deposited on each of 10 groups of three strips and the total dose of gamma

irradiation received by the strips.

TABLE VII

Group I:3ug/cm^2, no gamma exposure

Group II:3ug/cm^2, 3.5 - 4.0 Mrad

Group III:5ug/cm^2, no gamma exposure

Group IV:5ug/cm^2, 3.5 - 4.0 Mrad

Group V:10ug/cm^2, no gamma exposure

Group VI10ug/cm^2, 3.5 - 4.0 Mrad

Group VII:15ug/cm^2, no gamma exposure

Group VIII:15ug/cm^2, 3.5 - 4.0 Mrad

Group IX:50ug/cm^2, no gamma exposure

Group X:50ug/cm^2, 3.5 - 4.0 Mrad

Each of the thirty strips were soaked in aqueous solutions of 20 wt% NaCl to extract all stearylkonium heparin which was not chemically bonded to the polyvinylchloride. The aqueous solutions were then assayed for heparin using X_a inhibition assay. Table VIII illustrates the amount of heparin which was not extracted by the soaking procedure for each of the samples. This amount is the amount retained and bonded to the polyvinylchloride samples.

TABLE VIII

Samples	Detected in NaCl solution - (ug/cm2)	Percent Retained on PVC
Group I	3.5 ± 0.5	
Group II	1.2 ± 0.366 ± 9	
Group III	2.6 ± 0.5	
Group IV	1.1 ± 0.258 ± 8	
Group V	4.7 ± 0.6	
Group VI	3.3 ± 0.830 ± 17	
Group VII	11.8 ± 1.7	
Group VIII	10.2 ± 1.714 ± 14	
Group IX	43.5 ± 3.2	
Group X	42.2 ± 5.0 3 ± 11	

These results strongly indicate that heparin is not extracted from the surface of the polyvinylchloride but is retained or chemically bonded to the surface of the polyvinylchloride.

EXAMPLE 8

Polyvinylchloride (PVC) articles were soaked for 15 seconds with a Freon TE® solution of 0.5 wt% stearylkonium heparin. Half the articles were exposed to 3.5 - 4.0 megarads of gamma irradiation. Additionally, an equal number of polyvinylchloride articles were not soaked in the stearylkonium heparin solution. Of these, half were exposed to 3.5 - 4.0 megarads of gamma irradiation. Table IX illustrates each group of samples and their treatments.

TABLE IX

Group I: PVC 3/8", no gamma exposure

Group II: PVC 3/8", with 3.5 = 4.0 mrad

Group III: PVC 3/8", stearylkonium heparin treated, no gamma exposure

Group IV: PVC 3/8", stearylkonium heparin treated, with 3.5 - 4.0 Mrad

All of the polyvinylchloride articles were filled with 3.0 mL of non-heparinized bovine blood at 37° C and the blood was observed for the amount of time required to coagulate. Table X illustrates the coagulation time for each group of samples.

TABLE X

Coagulation Time of Fresh Non-heparinized Bovine Blood for PVC samples

Sample	Coagulation Time (min)		
Group I--	38,	50	
Group II	45,	47,	54
Group III	>60*,	>75,	>75
Group IV	>75,	>75,	>75

* sample stopped after 60 minutes

The results indicate that stearylkonium heparin coated polyvinylchloride is effective for extending the blood clotting time of bovine blood in contact with the coated PVC.

EXAMPLE 9

Four 10 foot segments of polyvinylchloride tubing having a O.D. of 3/8" were coated with stearylkonium heparin by flushing and draining the tubing with a Freon TE® solution of 0.5 wt% stearylkonium heparin. Two of the 10 foot segments were exposed to a total dose of 3.5 - 4.0 megarads of gamma irradiation. Each of the 10 foot segments was then leached with a 20 wt% NaCl solution by flowing the solution through the tubing at 4 liters/minutes for 2 hours. The solutions were then assayed for heparin using a chemical assay method which depends upon heparin complexing with Azure A dye. The solutions used to leach the nonirradiated samples contained enough heparin to correspond to a surface coverage of 4.1 micrograms/cM^2. The solutions used to leach the irradiated samples showed no heparin. The results of this test indicates that heparin which was coated on the tubing samples which were irradiated was not leached off but remains bonded to the surface.

Having thus described exemplary embodiments of the present invention, it should be noted by those skilled in the art that the disclosures herein are exemplary only and that alternatives, adaptations and modifications may be made within the scope of the present invention.

We Claim:

1.A process for reducing the surface thrombogenicity of polymeric materials, said process comprising the steps of:

providing polymeric material having a coating of heparin; and

exposing said coated polymeric material to sufficient ionizing radiation to chemically bind said heparin to said polymeric material.

2.The process of claim 1 wherein providing a polymeric material having a coating of heparin is accomplished by contacting surfaces of said polymeric material with an organic solvent solution of heparin for a length of time sufficient to deposit an anticoagulating amount of heparin on said surface of said polymeric material.

3.The process of claim 1 wherein said heparin is in the form of an organic compound-heparin complex.

4.The process of claim 3 wherein said organic compound-heparin complex is selected from the group consisting of organic cation-heparin-anion ionic complexes and organic base-heparin acid-base complexes.

5.The process of claim 4 wherein said organic cation-heparin anion ionic complex is a quaternary ammonium cation-heparin anion complex.

6.The process of claim 1 wherein said polymeric material is a biomaterial selected from the group consisting of polyvinylchloride, silicone, polyurethane, polyester, polyethylene, polycarbonate, polysulfone, polyacrylate, polypropylene, latex rubber, nylon and cellulose and its derivatives.

7.The process of claim 1 wherein said amount of radiation sufficient to chemically bind heparin to said polymeric material is at least 0.1 megarads.

8.The process of claim 1 wherein chemically binding said heparin to said polymeric material is covalently binding said heparin to said polymeric material.

9.A process for chemically binding heparin to medical devices, said process comprising the steps of:

forming a coating of an organic solvent and an organic compound-heparin complex on said medical device;

allowing said organic solvent to vaporize; and

exposing said coated medical device to ionizing radiation of at least 0.1 megarads.

10.The process of claim 9 wherein said organic compound-heparin complex is a quaternary ammonium cation-heparin anion complex is selected from the group consisting of benzalkonium heparin, stearylkonium heparin, and tridodecylmethylammonium heparin.

11.The process of claim 10 wherein forming a coating of said quaternary ammonium cation-heparin complex on said medical device is accomplished by flushing at least one surface of said medical device with an organic solvent solution of said complex of quaternary ammonium cation-heparin anion complex for a length of time sufficient to deposit an anticoagulating amount of said complex on said at least one surface.

12.The process of claim 11 wherein said surfaces of said medical device are blood contacting surfaces.

13.The process of claim 9 wherein said medical device is

comprised of biomaterials selected from the group consisting of silicone, polyvinylchloride, polyesters, polyurethanes, polypropylene, polyethylene, polysulfone, polyacrylates, cellulose, nylon and rubber latex.

14.The process of claim 9 wherein said organic solvent solution is a 1,1,2 trichloro 1,2,2 trifluoroethane solution of from about 0.01 wt% to about 10 wt% of a quaternary ammonium-heparin complex selected from the group consisting of benzalkonium-heparin, stearylkonium heparin, and tridodecylmethylammonium heparin.

15.The process of claim 9 further including the step of contacting said radiation exposed medical device with an aqueous salt solution having an ionic strength sufficiently high to exchange said quaternary ammonium cation with a cation of said aqueous salt solution.

16.The process of claim 14 further including the step of sterilizing said medical device.

17.The process of claim 16 wherein sterilizing said medical device is accomplished with ionizing radiation.

18.A process for simultaneously sterilizing a medical device and chemically binding heparin to said medical device, said process comprising the steps of:

forming a coating of an organic solvent and a quaternary ammonium cation-heparin anion complex on at least one surface of said medical device;

allowing said organic solvent to vaporize; and

exposing said coated medical device to ionizing radiation, said ionizing radiation being sufficient to chemically bind said quaternary ammonium cation-heparin anion complex to said medical device and to sterilize said

device.

19.The process of claim 18 wherein said quaternary ammonium cation-heparin anion complex is selected from the group consisting of benzalkonium heparin, stearylkonium heparin, and tridodecylmethylammonium heparin.

20.The process of claim 18 wherein forming a coating of said quaternary ammonium cation-heparin anion complex on said at least one surface of said medical device is accomplished by flushing said at least one surface of said medical device with an organic solvent solution of about 0.5 wt% of said quaternary ammonium cation-heparin anion complex for a length of time sufficient to deposit an anticoagulating amount of said complex on said at least one surface.

21.The process of claim 18 wherein said medical device is comprised of biomaterials selected from the group consisting of silicone, polyvinylchloride, polyesters, polyurethanes, polypropylene, polyethylene, nylon, acrylate, polysulfone, rubber latex and cellulose.

22.The process of claim 20 wherein said organic solvent solution is a 1,1,2 trichloro 1,2,2 trifluoroethane solution of from about 0.01 wt% to about 10 wt% of a quaternary ammonium heparin complex selected from the group consisting of benzalkonium-heparin, stearylkonium heparin, and tridodecylmethylammonium-heparin.

23.The process of claim 18 wherein said sufficient ionizing radiation is at least 1.5 megarads.

24.The process of claim 18 further including the step of packaging said coated medical device in sterile packaging

subsequent to allowing said organic solvent to vaporize.

25.An antithrombogenic medical device, said medical device comprising one or more biomaterials having a uniform and continuous coating of heparin, said heparin being chemically bonded to surfaces of said biomaterial by ionizing radiation.

26.The antithrombogenic medical device of claim 25 wherein said heparin is in the form of an ionic complex of a quaternary ammonium cation and heparin anion, said quaternary ammonium cation selected from the group consisting of benzalkonium heparin, stearylkonium heparin, and tridodecylmethylammonium heparin.

27.The antithrombogenic device of claim 25 wherein said biomaterials is selected from the group consisting of polyvinylchloride, polyurethane, silicone, polyesters, polyurethanes, polypropylene, nylon, polyacrylate, polysulfone, rubber latex, and cellulose.

28.The antithrombogenic device of claim 26 wherein said quaternary ammonium cation is removed from said biomaterials by exchanging with a cation of an aqueous salt solution.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/07661

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 L 33/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	Biomat., Med. Dev., Art. Org., vol. 2, no. 2, 1974, A.S. CHAWLA et al.: "Nonthrombogenic surface by radiation grafting of heparin: preparation, in-vitro and in-vivo studies", pages 157-169, see the whole document	1-28
X	GB,A,1136669 (DOW CORNING CORP.) 11 December 1968, see page 1, lines 56-72; page 2, lines 4-86	1-2,6-8
Y		3-5,9-28
Y	EP,A,0124200 (BECTON, DICKINSON AND CO.) 7 November 1984, see claims	3-5,9-28

-/-

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family.

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27-11-1992	25.01.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A,3453194 (D.R. BENNETT et al.) 1 July 1969, see claims	1-2,6-8
X	Polym. Plast. Technol. Eng., vol. 16, no. 2, 1981, J.E. WILSON: "Heparinized polymers as thromboresistant biomaterials", pages 119-208, see page 201	1
A	Radiation Research, vol. 45, 1971, Academic Press, Inc., F. JOOYANDEH et al.: "Chemical effects of gamma-irradiation of aqueous solutions of heparin and keratan sulphate", pages 455-461	
A	EP,A,0149693 (HONEYWELL MEDICAL ELECTRONICS B.V.) 31 July 1985	
A	WO,A,9101767 (BAXTER INTERNATIONAL INC.) 21 February 1991	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9207661 SA 64766

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 05/01/93 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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		EP-A-	0484393	13-05-92